

## RESEARCH ON THE EFFECTS OF MICROGRAVITY ON THE MUSCULOSKELETAL SYSTEM

NIH GUIDE, Volume 22, Number 21, June 11, 1993

PA NUMBER: PA-93-094

P.T. 34

### Keywords:

Musculoskeletal System

Biomechanics

Physiology, Human

Pathogenesis

National Institute of Arthritis and Musculoskeletal and Skin Diseases

### PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), in collaboration with the Life Sciences Division of the National Aeronautics and Space Administration (NASA), invites grant applications on basic, applied, and clinical research projects focusing on the effects of microgravity on the musculoskeletal system.

### HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Program Announcement (PA), Research on the Effects of Microgravity on the Musculoskeletal System, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

## ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, non-profit and for-profit, public and private organizations, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) Award (R29). Applications from minority individuals and women are encouraged.

## MECHANISMS OF SUPPORT

Support will be offered through regular research project grants (R01) and FIRST Awards (R29). Because the nature and scope of the research proposed in response to this PA may vary, it is anticipated that the size of an award will vary also.

## RESEARCH OBJECTIVES

Space travel encompasses many technological challenges and opportunities. As the U.S. Space Program prepares for extended duration space flights on the Space Shuttle, Space Station Freedom, and on exploration missions to the Moon and Mars, it is important that life sciences research provide a thorough understanding of the many physiologic changes that occur in a microgravity environment. Prolonged exposure to weightlessness diminishes functional capacity, performance and endurance of the musculoskeletal system, even at submaximal loads, and thus elicits concern about the health and well-being of space travellers, especially as space flight is extended in time. This research should also lead to development of effective countermeasures to any effects that may be detrimental to the functional capacity, health, or well-being of crew members.

The musculoskeletal system has the capacity to adapt its structural and functional properties in accordance with the type and degree of stimuli imposed on it. Prolonged space travel is essentially a period of significant unloading of the musculoskeletal system. Exposure to weightlessness results in structural and functional adaptations that place the musculoskeletal system on the low end of the continuum ranging from complete disuse to maximal load-bearing. Evidence from previous space flights and ground-based research indicates that the musculoskeletal system is functionally impaired with increasing duration of weightlessness.

Space flight has been consistently accompanied by loss of bone and negative calcium balance. Bone density may decrease by as much as 10 percent per year. This change in bone density is preceded by significant and more rapid weakening and atrophy of skeletal muscle.

A workshop on the "Effects of Space Travel on the Musculoskeletal System" was co-sponsored by the NIAMS and NASA in October 1990. The workshop provided state-of-the-art knowledge, identified research gaps and windows of opportunity, and recommended future directions for research on understanding the musculoskeletal system's adaptation to exposure to weightlessness, including development of adequate physiologic and performance-based countermeasures. Although there is a research base of some knowledge on the complex bone remodeling process and potential biological agents and factors that may be able to restore or prevent bone loss on earth, more research is required in space applications of these technologies. Considerably less information is available on understanding how force development by skeletal muscle is essential in maintaining bone integrity. Likewise, there is a strong science base regarding muscle physiology, but knowledge in microgravity environments is limited. A workshop summary, The Effects of Space Travel on the Musculoskeletal System, has been published (NIH Publication No. 93-3482, November 1992) and is available upon request from the Program Officials listed under

#### INQUIRIES.

The NIAMS, in collaboration with NASA, is interested in soliciting grant applications whose research focus is on the effects of microgravity on the musculoskeletal system.

The major objective of this Program Announcement is to stimulate basic, applied, and clinical research on elucidating the effects of microgravity on the musculoskeletal system. Development of mechanism-related hypotheses encompassing both basic and applied science is desirable. While the research focus is on reduced gravity conditions, well justified studies on musculoskeletal responses to increased gravity conditions may be instrumental in understanding the pathogenesis of bone and skeletal muscle weakness and loss during exposure to microgravity environments. A key feature of the basic research component is understanding the cellular mechanisms whereby alterations in the musculoskeletal system are evoked in response to external loading and loading histories. For example, how does loading or lack of it affect cellular processes and regulatory factors that control turnover of matrix and contractile proteins? Basic research would focus on the physiologic changes of bone and skeletal muscle in cell and tissue cultures that occur in a low or high gravity environment.

Applicants are also encouraged for appropriate applied/clinical studies addressing microgravity-induced osteopenia and skeletal muscle atrophy in whole animal and human experiments. Utilization of available technologies including, but not limited to, the following are encouraged: simulations of weightlessness (e.g., suspension limb model), centrifugation (alterations in 'g' forces), and bedrest. Applicants may collaborate with NASA scientists (based on availability of resources), especially in gaining access to hospital beds in a clinical setting and low or high gravity environment facilities.

Special emphasis should be placed on elucidating the etiology of the pathogenesis of bone loss and skeletal muscle weakness during exposure to an altered gravity environment and on research activities that will address the important issues of prevention and treatment of bone and skeletal muscle loss from microgravity exposure.

The research identified in this announcement is specifically targeted to the response of bone and muscle to alterations in environmental gravity that lead towards understanding the effects of space travel. Examples of research activities identified by the Workshop include, but are not limited to:

- o Quantification of rate, magnitude, and cellular origins of bone and skeletal muscle cell loss in conditions of altered gravity;
- o Influence of skeletal muscle second messengers on bone growth under microgravity environments;
- o Hormonal and growth factor effects on bone and muscle cell function and metabolism in relation to gravity effects;
- o Characterization of bone loading in bedrest subjects;
- o Bone and muscle cell responses to altered mechanical stress and gravity;
- o Evaluation of 3-D structure and integrity of the musculoskeletal system and constituent tissues in response to changes in gravity;
- o Bone and muscle cell expression, including characterization of cellular receptors, signal transduction and messengers in response to gravity changes;

- o Alterations in blood flow and its impact on cellular metabolism in microgravity; and
- o Development of therapeutic agents that restore bone loss and muscle weakness due to space travel.

These areas of research are neither prioritized nor meant to be restrictive. Investigators are encouraged to submit applications in any meritorious area of research responsive to the general research objectives of this Program Announcement.

## STUDY POPULATIONS

### SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study. Special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in form PHS 398 (rev. 9/91) in Sections 1-4 of the Research Plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans [including American Indians or Alaskan Natives], Asian/Pacific Islanders, Blacks, and Hispanics). The rationale for studies on single minority population groups must be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including, but not limited to, clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the review will be deferred until the information is provided.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

## APPLICATION PROCEDURES

Applications are to be submitted on grant application form PHS 398 (rev. 9/91). Applications will be accepted at the standard application deadlines indicated in the application kits.

Application kits are available at most institutional offices of sponsored research and may also be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone 301/435-0714. The title and number of the announcement must be typed in Section 2a on the face page of form PHS 398.

The completed original application and five legible copies of Form PHS 398 must be sent or delivered to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, MD 20892\*\*

## REVIEW PROCEDURES

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit by initial review groups of the Division of Research Grants. Following scientific-technical review, applications will receive a second-level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council or by other relevant advisory boards and/or councils.

## AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following criteria will be considered in the making of funding decisions:

- o Quality of the proposed project as determined by peer review;
- o Availability of funds; and
- o Program balance among research areas of the announcement.

## INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Inquiries regarding programmatic issues may be directed to:

Stephen L. Gordon, Ph.D.  
Musculoskeletal Diseases Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Westwood Building, Room 407  
Bethesda, MD 20892  
Telephone: (301) 594-9951

Richard W. Lymn, Ph.D.  
Muscle Biology Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Westwood Building, Room 403  
Bethesda, MD 20892  
Telephone: (301) 594-9959

Victor S. Schneider, M.D.  
Life Sciences Division  
National Aeronautics and Space Administration  
Code SBM  
300 E Street, SW  
Washington, DC 20546  
Telephone: (202) 358-2359

Direct inquiries regarding fiscal matters to:

Ms. Diane M. Watson  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Westwood Building, Room 732A  
Bethesda, MD 20892  
Telephone: (301) 594-9965

#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78<sup>th</sup> Congress, as amended, 42 USC 241) and administered under PHS grants policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.



---

[Return to 1993 Index](#)

[Return to NIH Guide Main Index](#)